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New Studies in Aromatic Chloromethylation

By

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Department of Chemistry
University of Durham

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A Thesis submitted for the degree of Master of Science at the University of Durham.

July 1992
Acknowledgements

I would like to thank my supervisor Dr M.R. Bryce for his encouragement and help. Also, Dr. S.T.A.K. Daley my industrial supervisor, without whose help this research would never have started. Finally to Seal Sands Chemical Co. Ltd. (Now Hexcel Chemical Products) for their financial support and generous time off work to do this thesis.

Declaration

The work described in this thesis was carried out by the author, in the Department of Chemistry, University of Durham. It has not been submitted previously for a degree at this or any other university.
Abstract

Chloromethylation reactions of anisole, cumene and trifluoromethylbenzene have been examined using the reagents formaldehyde and hydrogen chloride, in the presence of an extensive range of catalysts. Reaction conditions and choice of catalyst have been optimised to obtain a high ratio of chloromethylated product: diarylmethane product. For anisole this requires the use of titanium tetrachloride as catalyst at 0-50°C; for cumene, zinc chloride as catalyst at 42-48°C gives the best results. Trifluoromethylbenzene could not be chloromethylated using the HCl/CH₂O/ catalyst system.

Other alkoxybenzene substrates and chloromethylating reagents have been briefly studied.
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Chapter 1

Background to Aromatic Chloromethylation
1.1 General.

Chloromethylation is a method of directly substituting a hydrogen atom for a chloromethyl group in an aromatic structure. Its importance in synthetic chemistry lies in the versatility of the chloromethyl group to be converted into a wide range of other functional groups. (Scheme 1)

\[
\begin{align*}
&\text{ArCH}_2\text{CH}_2\text{NH}_2 \quad \overset{(1a)}{\rightarrow} \quad \text{ArCH}_2\text{CN} \quad \overset{(1b)}{\rightarrow} \quad \text{ArCH}_2\text{COOH} \\
&\quad \arrows{\text{ArCH}}_2\text{R} \quad (1) \quad \arrows{\text{ArCH}}_2\text{OH} \quad (2) \\
&\quad \arrows{\text{ArCH}}_2\text{OR} \quad (7) \quad \arrows{\text{ArCH}}_2\text{Cl} \quad (3) \quad \arrows{\text{ArCH}}_2\text{SH} \quad (4) \\
&\quad \arrows{\text{ArCH}}_2\text{Ar} \quad (5) \quad \arrows{\text{ArCHO}} \quad (5a) \quad \arrows{\text{ArCOOH}} \\
\end{align*}
\]

Scheme 1

Reagents: (1) NaCN (aq). (1a) H₂, Raney nickel. (1b) NaOH/H₂O₂.
(2) Na₂CO₃ (aq). (3) LiAlH₄. (4) NaSH. (5) Hexamine/H₂SO₄/MeOH. (5a) KMnO₄.
(6) Ar, AlCl₃. (7) ROH/KOH/DMSO. (8) R, AlCl₃.

The first published example of a chloromethylation reaction was by Grassi and Masselli in 1898.¹ They reported that the reaction of benzene with paraformaldehyde and hydrogen chloride in the presence of zinc chloride resulted in the formation of benzyl chloride.
In 1923 Blanc, using virtually the same method, also converted benzene to benzyl chloride. This aroused considerable interest in the reaction and also led to the name chloromethylation being given to this process.

Because chloromethylated aromatics are readily converted into a variety of species (see Scheme 1) this type of reaction is often an early step in a multistep synthesis, eg the manufacture of a drug. In addition to the efficiency of the reaction, the fact that paraformaldehyde and hydrogen chloride and both relatively inexpensive bulk materials gives the chloromethylation reaction great industrial importance. A good example of a drug synthesis using chloromethylation as a key step is the preparation of the coronary vasodilator verapamil (Scheme 2).
The chloromethylation reaction can also be performed by chloromethylethers.\textsuperscript{4,5} This reaction can be used in the manufacture of ion exchange resins, eg, the preparation of chloromethylated polystyrene.\textsuperscript{6}
Bis(chloromethyl)ether (BCME) is present in paraformaldehyde/hydrogen chloride reactions, and is a known carcinogen. This is one reason why alternative “safe” chloromethylation reagents are being sought. Such compounds include longer chain chloromethyl ethers which are claimed to be of lower volatility.

Another recently published procedure that provides an alternative to traditional chloromethylation uses methoxyacetyl chloride with aluminium trichloride as catalyst in nitromethane or carbon disulphide.

1.2 Chloromethylation using formaldehyde and hydrogen chloride

Formaldehyde (which may be in the form of paraformaldehyde, formalin or 1,3,5- trioxane) and hydrogen chloride are the most common reactants in the chloromethylation reaction. The conditions vary according to the type of compound to be chloromethylated.

Zinc chloride is the most common catalyst, however, aluminium chloride and tin(IV) chloride have also been used. It should be noted that in certain cases no catalyst is needed. This is when the aromatic ring has been activated by electron-donating groups such as a methoxy group.

Other non-metallic catalysts employed are protic acids such as sulphuric, phosphoric and acetic acid.

Although the present work addresses chloromethylation of benzene derivatives the reaction may also be used on heterocycles such as thiophene, 2-phenylbenzofuran and 1,2,5-thiadiazole.

The mechanism of chloromethylation is a typical electrophilic substitution. However, the exact structure of the electrophile used in this process has never been unambiguously established.
There have been many theories put forward for the mechanism of chloromethylation with formaldehyde and hydrogen chloride. Darzens\textsuperscript{18} considered that chloromethylacetate, CICH\textsubscript{2}O(O)CCH\textsubscript{3}, was the chloromethylating species when the reaction was carried out in acetic acid. Brown and Nelson\textsuperscript{19} however, reacted this ester with benzene in the presence of zinc chloride at 75-80\textdegree{}C for 16 hours, and significantly, no benzyl chloride was formed!

Dichloromethane can be formed by the reaction of formaldehyde and hydrogen chloride. When an attempt was made to chloromethylate benzene with dichloromethane in the presence of zinc chloride this also proved unsuccessful\textsuperscript{20}.

Two theories which involve ionic mechanisms have been put forward to explain the chloromethylation reaction. The attacking species could be [CH\textsubscript{2}Cl]\textsuperscript{+} which could be formed in the following reaction scheme\textsuperscript{21} (Scheme 4).

\[
\begin{align*}
\text{CH}_2\text{O} + \text{HCl} + \text{H}^+ & \xrightarrow{R_1} \text{CH}_2\text{OHCl} + \text{H}^+ \xrightarrow{R_2} \text{CH}_2\text{Cl} + \text{H}_2\text{O} \\
\text{ArH} + \text{CH}_2\text{Cl} & \xrightarrow{r} \text{ArCH}_2\text{Cl} + \text{H}^+
\end{align*}
\]

\textbf{Scheme 4}

If this scheme was true the rate of reaction would be described as follows:
However, Scheme 4 does not tie in with experimental data.\textsuperscript{22} When the reaction is carried out in H\textsubscript{2}SO\textsubscript{4} in the presence of LiCl, the chloride ion does not effect the rate of reaction. As the above rate equation includes the concentration of HCl this should not be so.

Another ionic mechanism proposes the formation of the intermediate hydroxymethyl cation \([\text{CH}_2\text{OH}]^+\). This electrophilic species would then attack the aromatic ring followed by replacement of the hydroxy group by a chlorine atom. A strong point in favour of this mechanism is that it has been shown that under chloromethylation conditions the hydroxy group in benzylalcohol is fully substituted by chlorine.\textsuperscript{23}

Therefore the following mechanism was proposed\textsuperscript{24}, (Scheme 5).

\[
\begin{align*}
\text{CH}_2\text{O} + \text{H}^+ & \quad \text{fast} \quad \rightarrow \quad \text{+CH}_2\text{OH} \\
\text{ArH} + \text{+CH}_2\text{OH} & \quad \text{slow} \quad \rightarrow \quad \left[ \text{+ArHCH}_2\text{OH} \right] \\
\left[ \text{+ArHCH}_2\text{OH} \right] & \quad \rightarrow \quad \text{ArCH}_2\text{OH} + \text{H}^+ \\
\text{ArCH}_2\text{OH} + \text{HCl} & \quad \text{fast} \quad \rightarrow \quad \text{ArCH}_2\text{Cl} + \text{H}_2\text{O}
\end{align*}
\]

Scheme 5

If, as postulated, the rate limiting step is the addition of the protonated form of formaldehyde to the aromatic reactant, the rate of reaction can be expressed as follows:
dx = k[ArH][CH2OH] = kK[ArH][CH2O][H+] 
dt

= KF[ArH][CH2O]

k= is the rate constant, K=equilibrium constant and KF= kK[H+]

As has been previously stated, it is usual with chloromethylation using formaldehyde and hydrogen chloride to employ a Lewis acid catalyst, often zinc chloride. The reaction mechanism using these reactants can be represented as follows, (Scheme 6).

\[
CH_2O + HCl + ZnCl_2 \rightarrow [CH_2OH]^+ [ZnCl_3]^- \\
ArH + [CH_2OH]^+ [ZnCl_3]^- \rightarrow \text{ArCH}_2 + ZnCl_2 + H_2O
\]

or:

\[
\delta^+ CH_2O + \delta^- ZnCl_2 + \text{Ar} \rightarrow Cl_2Zn'\text{OCH}_2 \rightarrow \text{ArCH}_2 + H_2O + ZnCl_2
\]

Scheme 6

Although this theory has been proposed some doubt has been cast on this theory by Olah\textsuperscript{25}. He has demonstrated that protonated chloromethyl alcohol is stable at temperatures below -65°C. Because of this he has suggested that this species is the reactive intermediate in the chloromethylation reaction.

As already mentioned, (Scheme 1), the chloromethyl group can be easily converted into other functional groups. It is therefore, not too surprising that a side reaction frequently occurs in the chloromethylation process, namely the formation
of diarylmethanes. This is thought to be a result of the reaction of chloromethylated product with another aromatic molecule. (Scheme 7) This could be thought of as Friedel Crafts alkylation.

\[ \text{Scheme 7} \]

This is usually an unwanted side reaction as it reduces the yield of the required chloromethylated product. There are many factors that can encourage the formation of this unwanted by-product.

1) Temperature: higher temperatures tend to increase diarylmethane formation.

2) Concentration of products: a point can be reached where more diarylmethane product will be formed than chloromethylated product if the reaction is allowed to proceed.

3) Choice of catalysts: aluminium chloride in particular is known to favour formation of diarylmethane products.

All these factors show how important it is to select the right reaction conditions and catalyst in order to maximize the yield of the chloromethylated product.
1.3 Chloromethylation using Chloromethylethers

Apart from chloromethylation using formaldehyde and hydrogen chloride, the other important chloromethylation reagents are chloromethylethers. It is well known that the action of hydrogen chloride on formaldehyde produces one of these compounds, bis(chloromethyl)ether (BCME). Indeed at one time it was thought that this could be the chloromethylating species itself.

The first chloromethylation using alkyl chloromethyl ethers was described by Sommelet in 1913. By the treatment of benzene with monohalogenoalkyl ethers in the presence of AlCl₃ in CS₂, he obtained a mixture of benzyl ether and benzyl chloride. He believed that the ether which is initially formed is then readily converted into the chloromethyl derivative through the action of HCl liberated during the reaction (Scheme 8).

\[
\text{ArH} + \text{ClCH}_2\text{OR} \xrightarrow{\text{AlCl}_3, \text{CS}_2} \text{ArCH}_2\text{OR} \\
\text{ArCH}_2\text{OR} \xrightarrow{\text{HCl}} \text{ArCH}_2\text{Cl}
\]

**SCHEME 8**

More recently, chloromethylation using chloromethyl ethers has been used industrially in the manufacture of ion-exchange resins. In particular polystyrene has been chloromethylated in this process, the chloromethyl group largely entering at the para position. This reaction produces a further side reaction where the polymer chains are cross-linked via methylene bridges. This is akin to diarylmethane formation discussed in section 1.2.
Other work has been done using chloromethyl ethers specifically to stop the formation of the carcinogen BCME (see section 1.1). Warshawsky et al. have stated that the preparation of chloromethyl octyl ether, by the action of hydrogen chloride on formaldehyde reacting with octanol, produced no BCME. The subsequent product was reacted with a variety of compounds in the presence of tin(IV) chloride to produce chloromethylated products. Unlike reactions with formaldehyde and hydrogen chloride, tin(IV) chloride is the preferred catalyst for this type of reaction.

Unlike chloromethylation using formaldehyde and hydrogen chloride, there has been little kinetic data on the reactions of aromatic compounds with chloromethylethers. Because of this, the picture on the mechanistic path of the reaction is unclear.

Two pathways are possible. Firstly, cleavage of the C-O bond under the influence of a protic or an aprotic acid. This would yield the chloromethylating cationic species +CH₂Cl₂.

The other mechanism would involve the chloromethyl ether being an alkylating agent. The alkoxy methyl derivatives would then be cleaved by HCl evolved in this step (Scheme 9).

\[ \text{ArH} + \text{ClCH}_2\text{OR} \rightarrow \text{ArCH}_2\text{OR} + \text{HCl} \]
\[ \downarrow \]
\[ \text{ArCH}_2\text{Cl} + \text{ROH} \]

Scheme 9

The second proposed pathway seems the more plausible as it is known that monochloromethylether (MCME) is difficult to cleave using aluminium chloride (3% yield after 100 hours at 55°C).
1.4 Chloromethylation of deactivated compounds

When chloromethylating deactivated aromatics, sulphuric acid is often used in the reaction mixture in conjunction with formaldehyde and hydrogen chloride\textsuperscript{31}. In other cases, the reaction is done in the absence of hydrogen chloride. The chloromethylation is performed in this case using paraformaldehyde, chlorosulphonic acid and concentrated sulphuric acid.\textsuperscript{32} This method is obviously limited to deactivated compounds as with more activated species sulphonation readily occurs.
Chapter 2
2.1.1 Introduction

Chloromethylation of a Range of Substituted Benzene Derivatives using Hydrogen Chloride and Paraformaldehyde

We have undertaken an extensive study of chloromethylation using a range of substituted benzene derivatives. Our aim was to build on the established HCl/CH₂O methodology (section 1.2) and especially to extend the range of the catalyst used for this reaction. Furthermore, no comprehensive survey had been published concerning the effects of systematically modifying the conditions of the reaction (i.e. temperature, reaction time, ratio of reactants, etc).

Of particular interest was the desire to find the optimum conditions and catalyst for maximizing the yield of chloromethylated product and minimising the formation of undesired side products, such as diarylmethanes.

We chose three substrates for these studies:

1. Anisole (1)
   - \( 
   \begin{array}{c}
   \text{C}_6\text{H}_4 \text{OMe} \\
   \end{array} 
   \)

2. Cumene (2)
   - \( 
   \begin{array}{c}
   \text{C}_6\text{H}_5 \text{CMe}_2 \\
   \end{array} 
   \)

3. Trifluoromethylbenzene (3)
   - \( 
   \begin{array}{c}
   \text{C}_6\text{H}_4 \text{CF}_3 \\
   \end{array} 
   \)

These compounds were all known to undergo chloromethylation and the substituents should modify the electronic properties of the benzene ring and, hence, have a marked effect on the course of the reaction. The methoxy group will strongly activate the ring to electrophilic substitution; the isopropyl group less so,
and the trifluoromethyl group will deactivate the ring. Thus more forcing conditions should be required to chloromethylate this last molecule.

By having these substituents which should act quite differently, we hoped to be able to categorize the different catalysts into a “league of reactivity”. This could enable the optimum catalyst to be chosen according to the nature of the substituent attached to the benzene ring.

The results will now be presented for each of the three substrates (1)-(3) in turn. Methoxybenzene and cumene have been extensively studied, trifluoromethylbenzene less so. The reason for this will become apparent when the results are presented.

The progress of each reaction was monitored by 60MHz ¹H N.M.R. spectroscopy. Final products were analysed by 250MHz ¹H N.M.R. spectroscopy which enabled the structure of the products to be unambiguously assigned and isomer ratios to be calculated (where appropriate).

2.1.2 Methoxybenzene

Precedents showed that this electron rich aromatic molecule was highly reactive towards hydrogen chloride and formaldehyde. Our initial conditions were to react methoxybenzene with formaldehyde and anhydrous hydrogen chloride in the presence of a range of catalysts at room temperature. However, if the temperature at which the gas was added was lowered to 0-10°C, the ratio of chloromethyl to diarylmethane products increased. Hence we arrived at the following standard reaction conditions.

To a stirred mixture of methoxybenzene, paraformaldehyde and cyclohexane at 20°C was added the catalyst. The temperature was then lowered to 0-10°C. Anhydrous hydrogen chloride was then added over a period of 2 hours. After the addition of the hydrogen chloride the temperature was allowed to rise to
room temperature. The reaction was stopped when no more chloromethyl product was being formed.

The results of the reactions are presented in Table 1:

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Product X</th>
<th>Product Y</th>
<th>Starting Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl₄</td>
<td>95</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Ti(OPr)₄</td>
<td>92</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>(Ph)₃CCl</td>
<td>44</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>HgCl₂</td>
<td>35</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>ScCl₃</td>
<td>33</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>SmCl₃</td>
<td>31</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>NONE</td>
<td>26</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>VCl₃</td>
<td>25</td>
<td>8</td>
<td>67</td>
</tr>
<tr>
<td>CoCl₂</td>
<td>24</td>
<td>47</td>
<td>29</td>
</tr>
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<td>21</td>
<td>52</td>
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<td>ZrCl₄</td>
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<td>Br₂</td>
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<td>25</td>
</tr>
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<td>100</td>
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</tr>
<tr>
<td>AlCl₃</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>FeCl₃</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>
TABLE 1  Chloromethylation of methoxybenzene with a range of catalysts: ratio of products and unreacted starting material in the final reaction mixture. Product X = Chloromethyl methoxybenzene  
Product Y = Diarylmethane product or higher homologue

The isomer ratios of ortho substituted: para substituted chloromethyl product were 1:2, except for when TiCl₄ and Ti(OPr)₄ were used as catalyst. These catalysts gave exclusively the para isomer.

Boron containing species such as BF₃ and BCl₃ were considered for use as a catalyst for methoxybenzene but it was considered likely that they would act in a similar way to AlCl₃ which had given diarylmethane products. These catalysts can be classified as "Hard" lewis acids.³³

2.1.3 Cumene

From information gained from the industrial manufacture of cuminyl chloride it was known that the chloromethylation of cumene requires a higher temperature than that for the chloromethylation of methoxybenzene. Our standard reaction conditions for cumene were as follows:

Add paraformaldehyde and a catalyst with stirring to a flask containing cumene. Heat the mixture to 42-48°C, then add anhydrous hydrogen chloride over 2 hours. The temperature was then maintained at 42-48°C until the reaction was complete. The results of the reactions are presented in Table 2. The ratio of ortho substituted to para substituted cuminyl chloride was 2:13.
<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Product X</th>
<th>Product Y</th>
<th>Starting material</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl₄</td>
<td>0</td>
<td>0</td>
<td>100</td>
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<tr>
<td>Ti(OP₃)₄</td>
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<td>100</td>
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<tr>
<td>(Ph)₃CCl</td>
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<td>0</td>
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<td>SmCl₂</td>
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<td>0</td>
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<tr>
<td>CoCl₂</td>
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<td>0</td>
<td>100</td>
</tr>
<tr>
<td>I₂</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 Chloromethylation of cumene with a range of catalysts: ratio of products and unreacted starting material in the final mixture. Product X = Cuminyl chloride, Product Y = Diarylmethane product or higher homologue
2.1.4 Trifluoromethyl benzene

We have been unable to find a literature precedent for the chloromethylation of this compound using a Lewis acid catalyst. We attempted the chloromethylation using catalysts which had been shown to form products with cumene (see Table 2). Table 3 shows the catalysts tried and the results of these reactions.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Temperature</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnCl₂</td>
<td>42-48°C</td>
<td>No reaction</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>42-48°C</td>
<td>No reaction</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>105-110°C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 3 Attempted chloromethylation of trifluoromethylbenzene

As no reference had been found using these catalysts the failure to observe any product formation under these conditions was not unexpected. We, felt, however, that these experiments were needed to illustrate the difference in reactivity of the substrates selected.

However, it is known that meta(chloromethyl)(trifluoromethyl)benzene is formed using chlorosulphonic acid as a reagent. We, therefore, did a series of reactions using this reagent where the temperature was varied. The conditions were as follows: Chlorosulphonic acid was added to a stirred mixture of paraformaldehyde, trifluoromethyl benzene and ethylene dichloride, (sulphuric acid could be used in place of ethylene dichloride with similar results) over
4 hours. The reaction mixture was then stirred for a further 16 hours. The results obtained are shown in table 4.

<table>
<thead>
<tr>
<th>Temp³C</th>
<th>Product X</th>
<th>Product Y</th>
<th>Starting material</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>42</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>5-10</td>
<td>34</td>
<td>26</td>
<td>40</td>
</tr>
<tr>
<td>10-15</td>
<td>26</td>
<td>21</td>
<td>53</td>
</tr>
<tr>
<td>15-20</td>
<td>23</td>
<td>19</td>
<td>58</td>
</tr>
</tbody>
</table>

**Table 4 Chloromethylation of trifluoromethylbenzene**

Product X=Chloromethyl trifluoromethyl benzene

Product Y=Diaryl methane product or higher homologue

If the order of addition of the reactants was changed, with the trifluoromethyl benzene being added last instead of the chlorosulphonic acid, the yield of the chloromethyl product would rise to 46%. The trifluoromethyl benzene was added over 4 hours. The reaction mixture was then stirred for a further 16 hours after which time no more chloromethyl compound was formed.
2.1.5 Comparison of different alkoxy compounds

A comparison was made between methoxybenzene, \( \text{\textit{n}} \)-butoxybenzene and \( \text{\textit{t}} \)-butoxybenzene\textsuperscript{34}, to see if the bulkier substituent on the oxygen would have any effect on the ortho/para ratios in the chloromethylated product. The reaction conditions were the same as for the methoxybenzene reaction with no added catalyst. The results are presented in Table 5.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product X</th>
<th>Product Y</th>
<th>Starting material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxybenzene</td>
<td>26</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>( \text{\textit{n}} )-Butoxybenzene</td>
<td>8</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td>( \text{\textit{t}} )-Butoxybenzene</td>
<td>0</td>
<td>100*</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5 Chloromethylation of a range of alkoxybenzenes.

Product X=Chloromethylated product

Product Y=Diarylmethane or higher homologue product

\*Or, alternatively, polymers derived from phenol.

\( \text{\textit{n}} \)-Butoxybenzene did not react any further even when stirring times were increased to 16 hours. The \( \text{\textit{t}} \)-butoxybenzene reaction mixture solidified after 1/2 of the gas addition, possibly due to the formation of polymer as the major product.
An experiment was also tried with dodecylbenzene. Under the conditions of the above reactions no product was seen. However when harsher conditions were used by doing the reaction under 3Bar pressure at 60-65°C a 90% yield of chloromethyl dodecyl benzene was achieved. We have not found any reference to a chloromethylation reaction being done under pressure. We believe that if the contents of the reaction mixture had not been contained BCME, which is likely to be formed initially, would have been lost through the top of the vessel due to the volatile nature of this compound.

2.1.6 Reaction profile

Two experiments were performed in order to follow the reaction profile for the formation of cuminyl chloride. These reactions were monitored by gas chromatography. The results, including the ortho/para ratios, are shown in Figures 1-4. The catalysts used were zinc chloride and ferric chloride. Zinc chloride was chosen as it had proved to be the best catalyst for chloromethylating cumene, and ferric chloride was chosen because it was known (Table 2) to form a mixture of chloromethyl and diarylmethane products.
Figure 1

Chloromethylation of cumene with Zinc chloride catalyst

Time (Hours)

% decrease

Cuminyl chloride
Cumene

Figure 1
Chloromethylation of cumene with Zinc chloride catalyst

Figure 2
Chloromethylation of cumene with Ferric chloride catalyst

Figure 3

--- Cuminyl chloride  --- Cumene
Chloromethylation of cumene with Ferric chloride catalyst

Figure 4
2.1.7 Bromomethylation

We were attracted by a report from Mitchell and Lyer. In this work various aromatic hydrocarbons were bromomethylated using 48% aqueous hydrobromic acid, glacial acetic acid, 1,3,5-trioxane and a phase transfer catalyst (tetradecyltrimethyl ammonium bromide).

It was claimed that this procedure produced yields of >90% of bromomethylated product with no diarylmethane products. For example, toluene yielded 96% of \( \beta \)-(bromomethyl)toluene. In our hands, under identical conditions, the yields obtained for bromomethylated product were in accordance with Mitchell and Lyer’s results (within experimental error). Also, we detected no diarylmethane product. However, our results differ significantly in that we obtain a significant amount of \( \alpha \)-(bromomethyl)toluene alongside the \( \beta \)-isomer. In our hands the ratio was \( \alpha : \beta = 2:5 \) which is in accordance with the low selectivity previously observed by other workers who chloromethylated toluene. This aspect of Mitchell and Lyer’s work should, therefore, be treated with circumspection.
2.1.8 Experiments with alternative chloromethylating reagents

All the chloromethylation reactions so far discussed involve hydrogen chloride and paraformaldehyde. We were interested in a claim by Warshawsky et al that he could make the chloromethylating reagent (4) by reacting a long chain primary alcohol with paraformaldehyde and hydrogen chloride and detect no BCME during the reaction.⁶

$$\text{(CH}_2\text{n)}\text{OCH}_2\text{Cl} \quad n = 4-12 \quad (4)$$

Even so, with paraformaldehyde and hydrogen chloride present there must still be an inherent danger of BCME formation.

We therefore made two possible chloromethylation reagents via a route that did not use paraformaldehyde and hydrogen chloride⁷. This would eliminate any possibility that the dangerous carcinogen BCME could be made.

The molecules were:

\[
\begin{align*}
\text{O} & \quad \text{N} - \text{CH}_2\text{Cl} & \quad \text{N}-\text{(chloromethyl)phthalimide} \quad (5) \\
\text{O} & \quad \text{Me} - \text{OCH}_2\text{Cl} & \quad \text{N}-\text{(chloromethyl)tosylate} \quad (6)
\end{align*}
\]
Disappointingly these reagents had no reactivity with either anisole or cumene using a range of catalysts.
2.2 Discussion of data

Examination of the data contained in Table 1 reveals the following features. The catalyst of choice for obtaining the chloromethylation product exclusively as the *para* isomer is TiCl₄. Coordination of titanium to oxygen is well known: this would sterically hinder the *ortho* position and, hence, lessen the activating effect of the methoxy group. The consequence of this is to reduce both *ortho* substitution and diaryl methane formation.

Another notable result occurs when I₂ is used as a catalyst. This appears to have the effect of supressing the reaction totally. This is, at first sight, surprising as no catalyst is actually needed to obtain a chloromethylation reaction with methoxybenzene (Table 1). We tentatively suggest that a redox reaction may be occurring in the presence of iodine, i.e. a single electron transfer to yield the anisole radical cation. This transient species could then possibly interfere with the reaction.

The more usual Lewis acid catalysts in Table 1, e.g. ZnCl₂, AlCl₃ and CdCl₂, promote diarylmethane formation (or higher homologues). Under these conditions the chloromethyl product is initially formed but quickly reacts to form diarylmethane products (Scheme 7). The catalysts seem to have further activated the aromatic molecule.

The most reactive catalyst for diarylmethane formation is ferric chloride. This reaction was notably very exothermic. No chloromethyl product could be detected in the resulting solid formed in this reaction.

As expected, cumene proved less reactive than methoxybenzene where the chloromethylation reaction is concerned. Zinc chloride proved to be the best
catalyst for the chloromethylation of cumene. This agrees with the literature precedents for chloromethylation of alkylbenzenes in general.

A comparison was made between ZnCl₂, ZnBr₂ and ZnI₂ to establish the effect of varying the halide ion on the reaction course. It must be assumed that after a period of gassing with hydrogen chloride, ZnBr₂ and ZnI₂ would have been converted to ZnCl₂. For ZnCl₂ and ZnBr₂, the results were the same within experimental error. However, with ZnI₂ as catalyst there was a reduction in the formation of chloromethyated product. This again could be due to the free I₂ suppressing the reaction as noted above with the reaction of I₂ with anisole.

From the outset it was clear that trifluoromethylbenzene was going to be the least reactive of our three aromatic substrates as the CF₃ substituent strongly deactivates the benzene ring to the reaction with electrophiles. Because of this, only our most reactive catalysts were chosen (see Table 3). However, they all failed to give any product whatsoever.

It is, however, possible to chloromethylate trifluoromethylbenzene as can be seen from the results in Table 4. At low temperatures chlorosulphonic acid and paraformaldehyde will react to chloromethylate trifluoromethylbenzene. Table 4 illustrates that 0°C is preferred to 20°C. For this reaction SO₃ is believed to be the catalyst. At a higher temperature, SO₃ could decompose, reducing the efficiency of the reaction. This particular method of chloromethylation has been successfully used on an industrial scale to manufacture trifluoromethylbenzylchloride, which is an agrochemical intermediate.³⁸

It was decided not to use chlorosulphonic acid with methoxybenzene or cumene as sulphonation of the aromatic nucleus would be expected to compete with the chloromethylation process.
In Table 5 it was observed that the attempt to chloromethylate 1-but oxybenzene produced no chloromethylated product, only a polymeric-type solid. The likely explanation for this could be the removal of the 1-butyl group under the acidic reaction conditions, to yield phenol. This could then polymerise to give the observed result.

The n-butoxybenzene reaction mixture was surprisingly low in chloromethylated product. It was hoped that the larger alkoxy group (relative to methoxy) would simply reduce the amount of ortho product and not stop the reaction. To further explore this surprising effect of the n-butoxy substituent, experiments would be needed with ethoxy and isopropoxy groups.

Significant differences in reactivity have been observed when comparing cumene with dodecylbenzene. The latter compound requires a more concentrated amount of ZnCl₂ catalyst (85% as compared to 60%). If the increase in chain length does reduce reactivity, then the n-butoxybenzene may require slightly more forcing conditions to induce the chloromethylation reaction to occur.

The reaction profile experiment showed the importance of choosing the correct catalyst in the chloromethylation reaction. In Figure 1 the catalyst zinc chloride helps in the formation of the chloromethyl product cuminyl chloride. In Figure 3 initially cuminyl chloride is formed. However as the reaction proceeds the diarylmethane reaction becomes the dominant reaction (Scheme 7). Figures 2 and 4 show that the ortho/para ratios remain constant throughout the reaction. This was not unexpected.
Chapter 3
Experimental

All samples unless stated were analysed by proton nuclear magnetic resonance spectroscopy. Routine spectra were obtained on a Hitachi-Perkin Elmer R24B 60 spectrometer, operating at 60 MHz. Finished product analysis was done on a Bruker AC250 machine operating at 250.134 MHz. Chemical shifts are quoted in ppm, relative to tetramethylsilane ($\delta_H=0.0$ ppm). Yields were calculated from these spectra by using the analysis of the starting mixture as a reference.

On reaction profile experiments the reaction mixture was analysed by capillary gas chromatography.
General Procedure

Chloromethylation of Methoxybenzene (Table 1)

Methoxybenzene (6.0g, 0.056 mmole) was charged to a 50ml two neck round bottom flask. To this was added paraformaldehyde (1.9g, 91%, 0.058mmole) and cyclohexane (4.0g). The mixture was then magnetically stirred and cooled to 0-10 °C. At this temperature HCl was added via a dip-pipe over 2 hours or until no more gas was absorbed. The reaction was then stirred for 5 hours, the temperature being allowed to rise to room temperature. Each reaction was scrubbed by dilute sodium hydroxide solution to prevent any acidic or BCME vapours being released into the fumehood. Each reaction was worked up in the following manner. The reaction mixture was added to water (10ml). The organic phase was then washed with sodium hydroxide (1M, 10ml), until the pH of the aqueous solution was > 7.

$^1$H NMR (CDCl₃): 3.46 (3H, s, O-CH₃), 4.46 (2H, s, CH₂Cl), 7.15-6.89, (4H, q, Ar)

Chloromethylation of Cumene (Table 2)

Cumene (4.0g, 0.033 mmole) was added to a 50ml two neck round bottom flask. To this was added paraformaldehyde (1.2g, 91%, 0.038mmole) and catalyst (0.011mmole). The mixture was magnetically stirred and heated to 42-48°C. HCl gas was added via a dip pipe to the mixture over 2 hours or until no more gas was being absorbed. The reaction was then stirred at 42-48°C for a period between 4-18 hours (see below), until the reaction was seen to be complete by proton N.M.R analysis. Each reaction was scrubbed by dilute sodium hydroxide solution to prevent any acidic or BCME vapours being released into the fumehood. Each reaction was worked up in the following manner. The reaction mixture was added to
water (10ml). The organic phase was then washed with sodium hydroxide (1M, 10ml), until the pH of the aqueous solution was > 7.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Stirout Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl₄</td>
<td>5 Hours</td>
</tr>
<tr>
<td>Ti(OPrᵢ)₄</td>
<td>5 Hours</td>
</tr>
<tr>
<td>(Ph)₃CCl</td>
<td>5 Hours</td>
</tr>
<tr>
<td>HgCl₂</td>
<td>5 Hours</td>
</tr>
<tr>
<td>ScCl₃</td>
<td>5 Hours</td>
</tr>
<tr>
<td>SmCl₃</td>
<td>5 Hours</td>
</tr>
<tr>
<td>None</td>
<td>5 Hours</td>
</tr>
<tr>
<td>VCl₃</td>
<td>5 Hours</td>
</tr>
<tr>
<td>CoCl₂</td>
<td>5 Hours</td>
</tr>
<tr>
<td>NiCl₂</td>
<td>5 Hours</td>
</tr>
<tr>
<td>TiCl₂</td>
<td>5 Hours</td>
</tr>
<tr>
<td>ZrCl₄</td>
<td>5 Hours</td>
</tr>
<tr>
<td>Br₂</td>
<td>5 Hours</td>
</tr>
<tr>
<td>I₂</td>
<td>5 Hours</td>
</tr>
<tr>
<td>SnCl₂</td>
<td>2 Hours</td>
</tr>
<tr>
<td>SnCl₄</td>
<td>2 Hours</td>
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<tr>
<td>CdCl₂</td>
<td>None</td>
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<tr>
<td>ZnBr₂</td>
<td>None</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>None</td>
</tr>
<tr>
<td>FeCl₃</td>
<td>None</td>
</tr>
</tbody>
</table>

¹H NMR (CDCl₃) : 1.22, 1.25, (6H, d, CH-CH₂) ; 2.85-2.96, (1H, m, CH-CH₂) ; 4.56, (2H, CH₂-Cl) 7.19, 7.22, 7.29, 7.32(4H, q, Ar).
Reactions of TrifluoromethylBenzene (Table 3)

Trifluoromethylbenzene (8.0g, 0.056mmole) was added to a 50ml round bottom flask. To it was added paraformaldehyde (1.9g, 91%, 0.058 mmole) and catalyst (0.0193mmole). The HCl was added to the mixture over 2 hours. The reaction was stirred for 6 hours. The temperature of the reaction was as shown in table 3. On each reaction no product was observed.

Reaction of Dodecylbenzene

Dodecylbenene (146g, 1mmole) was placed in a glass pressure vessel. To it was added zinc chloride (136.3g, 1mmole) diluted with water (24ml), and paraformaldehyde (33g, 91%, 1mmole). The temperature was then raised to 60-65°C when HCl (36.5 g, 1mmole) was added over 3 hours. The temperature was maintained between 60-65°C and the pressure was not allowed to rise above 3Bar for a total reaction time of 48 hours. The lower aqueous zinc chloride layer was separated from the product layer. The product was then washed with water (100ml) then sodium hydroxide solution (1 M, 100ml). Yield of product = 90%. (Yields were calculated from proton N.M.R spectra).

Reactions In Table 4

Chlorosulphonic acid (116.5g, 1mmole) was added to a stirred mixture of paraformaldehyde (91%, 33g, 1mmole), trifluoromethylbenzene (146g, 1mmole) and ethylene dichloride (100g) over 4 hours at temperatures varying between -5-0°C and 15-20°C (see Table 4). The reaction was then stirred for a further 16 hours at the addition temperature. The acidic lower layer was then separated from the organic product layer. The latter layer was then washed with water (100ml) followed
by sodium hydroxide solution (1M,100ml). The solvent was removed by evaporating under reduced pressure. Yields of products were calculated from proton N.M.R. spectra.

$^1$H NMR(CDC$_3$) : 4.60, (2H, s, CH$_2$-Cl); 7.46-7.65, (5H, Ar)

**Reaction Profile**

These experiments were carried out in the same manner as the reactions of Table 2. Samples were taken for analysis at 1 hourly intervals and were monitored by gas chromatography.

**Chloromethylation of n-Butoxybenzene**

n-Butoxybenzene (8.3g, 0.056 mmole) was charged to a 50ml two neck round bottom flask. To this was added paraformaldehyde (1.9g, 91%, 0.058mmole) and cyclohexane (4.0g). The mixture was then magnetically stirred and cooled to 0-10 °C. At this temperature HCl was added via a dip-pipe over 2 hours or until no more gas was absorbed. The reaction was then stirred for 16 hours, the temperature being allowed to rise to room temperature. The work procedure was the same as described for the analogous methoxybenzene reaction. Yields were calculated from N.M.R. spectra, (Table 5).

**Reaction of t-Butoxybenzene**

t-Butoxybenzene (8.3g, 0.056 mmole) was charged to a 50ml two neck round bottom flask. To this was added paraformaldehyde (1.9g, 91%, 0.058mmole) and of cyclohexane (4.0g). The mixture was then magnetically stirred and cooled
to 0-10 °C. At this temperature HCl was added via a dip-pipe. After 1/2 hour of the HCl addition the reaction mixture went solid.

Reactions of N-(Chloromethyl)phthalimide

Anisole (3.8g, 0.035mmole) was placed in a 50ml round bottom two neck flask. To this was added N-(chloromethyl)phthalimide (6.8g, 0.035mmole) dissolved in dichloromethane (60g). The temperature of reaction was varied between 0°C and 50°C. The catalyst used were AlCl₃, SnCl₄, TiCl₄ and ZnCl₂. No products peaks were observed by in the NMR spectra of the crude reaction mixture after removal of the solvent.
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